REMARKS

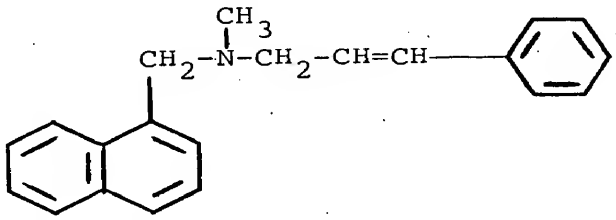
Claims 1-3 and 5-32 have been presented for examination, and claims 1-3, 5-11, 14-29 and 31 are now in the case. No additional fee is required.

Claims 1-3 of the present application are rejected under 35 USC 103 over Biniecki, et al (I) or Biniecki, et al (II) in view of Gunn, et al and Crossley (all of record). The Examiner argues that the primary references disclose N-phenethyl-N-methyl substituted naphthylmethyl amine derivatives closely related to the N-cinnamyl substituted compounds of the instant application and that the compounds are useful as muscle relaxants. The Examiner further argues that the secondary Gunn, et al reference discloses that phenethyl and cinnamyl moieties are not only structurally similar but are also pharmacologically similar. He notes that Applicant's arguments in the Amendment of September 17, 1979 on parent application Serial No. 1,479 filed January 8, 1979 have again been carefully considered but are not deemed to be persuasive of patentability. The Examiner concludes that while the instantly claimed compounds differ from the prior art in at most two respects, the differences are not patentably significant, since, allegedly, the art teaches that the substitution of cinnamyl for phenethyl would not produce unexpected results. The Examiner further notes that the difference in isomerism is also considered obvious in the absence of unexpected properties. The Examiner concludes that the combination of the primary and secondary references is proper, since the art compounds are muscle relaxants. Accordingly, no invention is seen in the instantly claimed compounds in view of

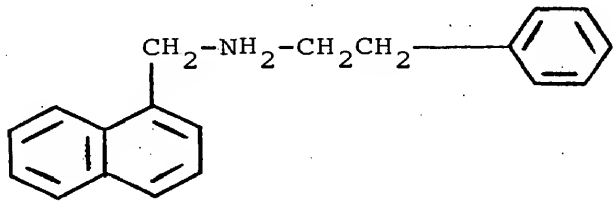
the equivalence of phenethylamine and cinnamylamine disclosed by the prior art in the absence of unexpected properties. Applicant respectfully disagrees and traverses the rejection.

For the purpose of commenting on the Examiner's statement that Applicant's compounds are closely related to the art compounds and differ from the art compound in at most two respects, Applicant has again set out below the closest compound from the present application and from the Biniecki, et al references.

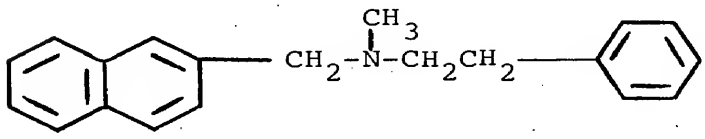
APPLICANT'S COMPOUND



ART COMPOUND I



ART COMPOUND II



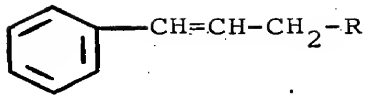
It will be noted immediately that the prior art compounds differ from Applicant's closest compound not in at most two respects but in at least three respects. The cinnamyl moiety itself differs in two respects from the phenethyl moiety. Its side chain is unsaturated, which permits isomerism, and contain three carbon atoms, while the phenethyl side chain is saturated and contains two carbon atoms. The third difference, as pointed out in the aforementioned amendment of September 17, 1979, is that art compound I is a secondary amine as opposed to the tertiary amine of the present application; and art compound II, which is a tertiary amine, is substituted at the 2-position of the naphthylene ring while Applicant's compound is substituted at the 1-position. There is clearly nothing in either of the Biniecki references which would suggest either the substitution of a cinnamyl moiety for the phenethyl moiety or the specific structural arrangement of the compound of the instant application. More importantly, there is nothing in the references which suggest that carrying out the manipulations necessary to transform the art compounds into Applicant's compound would result in a product having the antimycotic activity of the closest presently claimed compound.

The remaining compounds of the instant application have additional differences and are even further removed from any compound disclosed in the primary references. These compounds are, therefore, clearly patentable over the Biniecki compounds.

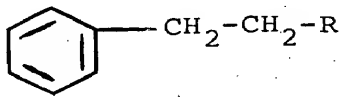
With regard to the Examiner's argument relating to the secondary Gunn, et al reference, Applicant does not believe

that it can properly be said that the reference teaches that phenethyl and cinnamyl derivatives are structurally and pharmacologically similar. The secondary reference actually states only that the two compounds, phenethylamine and cinnamylamine, have similar physiological activity; and it appears from the discussion on page 425 of the reference that the activity involved is CNS stimulant activity. This, contrary to the Examiner's comment, is not only different, but is completely opposite to the muscle relaxant activity of the primary references; and accordingly, the proposed combination of the primary reference with the Gunn secondary reference is, on its face, improper.

Phenethylamine and cinnamylamine are both primary amines; and it is clear that further substitution of the nitrogen atom to give secondary amines, or, as in the instant application, tertiary amines, would be expected by those skilled in the art to drastically and unpredictably affect their properties. It will be noted that the Gunn, et al reference, itself, discloses that when further changes are made in the overall structure of the molecule, as in the case of phenylbutenylamine and diphenylethylamine the physiological activity of the compounds become more dissimilar. This is also evidenced by the fact that when Gunn's phenethylamine is converted to Biniecki's derivatives its activity changes from a CNS stimulant to a CNS depressant; and when Gunn's cinnamylamine is converted to Applicant's compound, its activity changes from a CNS stimulant to antimycotic agent. It is clearly stretching the concept of equivalence beyond acceptable bounds to conclude that because cinnamylamine and phenethylamine have similar CNS stimulant properties, every compound of the formula

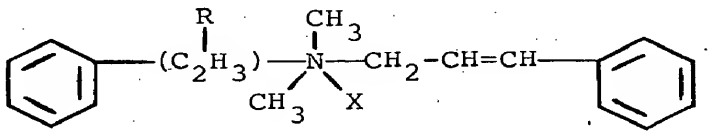


would be expected by one skilled in the art to have properties similar to every compound of the formula



regardless of the significance of R or the nature of the property. Applicant submits that the equivalency proposed by the Examiner would not be recognized by persons reasonably skilled in the antimycotic art and that the Examiner's argument based on the Gunn reference is clearly neither legally nor scientifically sound.

With regard to the Crossley patent, it is believed that this reference is cited by the Examiner solely to relate cinnamylamine derivatives to antiseptic and germicidal activity. The compounds disclosed in this patent are quaternary ammonium salts and have the following general structure



where R is an aliphatic radical of 8 to 12 carbon atoms and X is chlorine, bromine or iodine. These compounds are ionic in nature and are totally different structurally, chemically and pharmacologically from the covalent tertiary amines of the instant application. The antiseptic and germicidal activity disclosed in the reference is completely different and totally

unrelated to the antimycotic activity of the instantly claimed compounds. Applicant, therefore, submits that the ammonium salts of the Crossley reference clearly could not by any stretch of the imagination suggest combining the primary Biniecki references with the Gunn, et al reference to obtain the antimycotic compounds of the present application.

The Examiner has clearly used Applicant's disclosure as a guide in selecting primary and secondary references, which are directed to structurally and pharmaceutically unrelated compounds, and then has combined them in such a way as to synthesize the compounds of the present application without any indication in the references that such a combination would be desirable or would result in useful products. In Ex parte Koo (150 USPQ 131) the Board of Appeals, in more closely related compounds, found it improper to arbitrarily interchange substituents, even though the art in that case did contain a considerable number of references to support equivalence. Moreover, in In re Regal, Buchel and Plempel (188 USPQ 136), the Court of Customs and Patent Appeals reiterated its position that

> ". . . there must be some logical reason apparent from positive, concrete evidence of record which justifies a combination of primary and secondary references. . ." "The mere fact that it is possible to find two isolated disclosures which might be combined in such way to produce a new compound does not necessarily render such production obvious unless the art also contains something to suggest the desirability of the proposed combination".

Applicant submits that there is no logical reason even vaguely apparent in the present evidence of record which would justify

the combination of the primary and secondary references in the manner proposed by the Examiner.

In support of the patentability of the instantly claimed compounds, Applicant is again enclosing a copy of the Declaration Under 37 CFR 1.132 submitted with the aforementioned amendment of September 17, 1979 on patent application Serial No. 1,479. The Declaration compares the antimycotic activity of Applicant's compound (referred to as compound A in the Declaration) with art compound I (referred to as compound B in the Declaration), art compound II (referred to as compound D in the Declaration) and N-(2-naphthylmethyl)-N-(2-phenethyl)amine (referred to as compound C in the Declaration). Compound C is disclosed in the Biniecki II reference along with compound D.

From the results in the table on page 8 of the Declaration, it can be seen that Applicant's compound A is 500, and usually 1000 times more active than art compound B, C and D against various strains of dermatophytes. The results also show that compound A of the instant application is significantly more active than the prior art compounds against various fungus strains. The compounds of the primary reference are, for all practical purposes, inactive as antimycotic agents. The unexpected difference in activity of Applicant's compound versus the art compounds and the level of difference clearly rebuts the presumption of prima facie obviousness alleged by the Examiner. Applicant accordingly submits that the compounds of the present application are patentable over the prior art; and it is respectfully requested that the Examiner reconsider his rejection of the claims now in the application and withdraw it.

The Examiner requires the election of a single ultimate species from claims 7 to 11, 14 to 29 and 31 for further prosecution, since no generic claim has been found to be allowable. In accordance with the requirement, Applicant elects the compound of claim 7, on which claims 1-3, 5 and 6 also read, for further prosecution.

Applicant has amended claims 7 to 10 to insert the more appropriate title nomenclature of examples 1 to 4 and claims 11, 14 to 29 and 31 to provide the appropriate configurations set out in examples 5, 8-23 and 25. Applicant has also cancelled duplicate claims 12, 13, 30 and 32.

In view of the above amendments, comments and enclosed Declaration, it is believed that the instant application is now in condition for allowance; and, therefore, it is respectfully requested that the Examiner withdraw the rejection of the claims now in the case and pass the application to issue.

Respectfully submitted,

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September 5, 1980
Enc.: Declaration Under 37 CFR 1.132